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The reaction of pyrrole with dimethyl carbonate under phosphazene catalysis: *N*-methoxycarbonylation *vs N*-methylation

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ABSTRACT

Phosphazene (*t*-butylimino-tris(dimethylamino)phosphorane (P_1-*t*-Bu), *t*-butylimino-tris(pyrrolidino)-phosphorane (BTPP)) and amidine (1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)) superbases have been investigated as catalysts in the direct reaction of pyrrole with dimethyl carbonate (DMC). The system phosphazene/pyrrole/DMC proves to be a flexible synthetic tool, as it offers a solution not only for the direct and selective phosgene-free synthesis of 1-methoxycarbonyl pyrrole (**1**), but also for the straightforward and selective synthesis of 1-methylpyrrole (**2**) through a safer way which avoids the use of harmful methylating agents such as methyl halides and $(MeO)_2SO_2$. The influence of factors (temperature, catalyst loading, reaction time, etc.) affecting yields and selectivities has been investigated. We have also ascertained that a major reaction pathway to the formation of **2** involves the decarboxylation of the primary product **1**. Also this process was catalytically promoted by the phosphazene catalyst. Co-generated CO_2 opened a way to the deactivation of phosphazene catalyst, which converted mainly into catalytically inactive $OP(NR_2)_3$ (NR_2 = NMe_2, NC_4H_8).

1. Introduction

The development of new synthetic strategies characterized by high selectivity and able to replace hazardous reagents with benign compounds in chemical synthesis is one of main goals of modern chemical industry [1]. In the last few years great attention has been devoted to the synthetic utilization of dimethyl carbonate (DMC), a *safe harmless* chemical [2], currently produced, even on industrial scale, through routes (oxidative carbonylation of methanol, for instance) more eco-sustainable than the conventional phosgenation method [2,3]. As ambident electrophile, DMC can be utilized in organic synthesis as a potential eco-friendly carbonylating or methylating agent, respectively, in place of toxic phosgene or harmful methyl halides and dimethyl sulfate [2,4–16]. A lot of studies in this area have been concerned with the utilization of DMC for methoxycarbonylation or methylation of amines [2,16]. In comparison, much less is known on its use for the *N*-functionalisation of *N*-heteroaromatic compounds [14,17–20], as, for instance, pyrrole.

1-Methoxycarbonyl pyrrole (**1**) is unanimously recognized as an important synthetic intermediate in the preparation of a variety of chemicals (indoles; epibatidine and its derivatives or analogues (epiboxidine and other 7-azabicyclo[2.2.1]heptane derivatives); tropane alkaloids), most of which have pharmaceutical relevance or, more generally, are characterized by remarkable biological activity [21–32]. The traditional method of synthesis of **1** starts from harmful and hazardous phosgene. In fact, it is based on the use of toxic methylchloroformate (a phosgene-derivative) as methoxycarbonylating agent, and, moreover, requires the preliminary conversion of pyrrole into a more nucleophilic alkali pyrryl salt, which is reacted *in situ* with MeOC(O)Cl to give the target product [33–35]. A relatively more recent protocol, based on the activation of pyrrole-1-carboxylic acid through the intermediate formation of pyrrole-1-carboxylic acid anhydride [36], is atomically uneconomical as it involves a multistep procedure and needs 2 mol of pyrrole (for preforming the anhydride) *per* mol of product **1**.

Also 1-methylpyrrole (**2**) finds large practical application as starting reagent in many synthetic processes [37–41]. The traditional synthetic procedures for **2** involve the use, or formation *in situ*, of pyrryl salts and their reaction with conventional methylating agents (CH_3X, $(MeO)_2SO_2$)) [42–45].

The search for more direct selective eco-sustainable synthetic ways to **1** or **2**, which imply the use of halogen-free, non-toxic and safer starting materials, is, obviously, of great interest. A very appealing synthetic route to **1** and **2** is the *direct* reaction of pyrrole with DMC (Eqs. (1) and (2)). Obviously, a major problem related to this approach is the characterization of the factors that control the selectivity for the desired process (*N*-methoxycarbonylation or *N*-methylation) and, therefore, can favour the selective formation of

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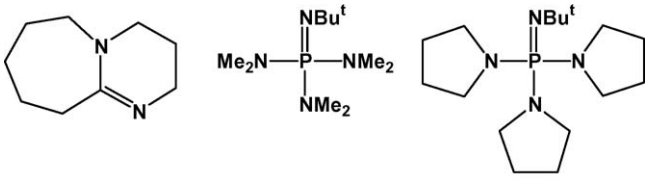
one product with respect to the other one.

$$\mathrm{HetNH} + (\mathrm{MeO})_2\mathrm{CO} \rightarrow \underset{(1)}{\mathrm{HetNC(O)OMe}} + \mathrm{MeOH} \quad (1)$$

$$\mathrm{HetNH} + (\mathrm{MeO})_2\mathrm{CO} \rightarrow \underset{(2)}{\mathrm{HetNMe}} + \mathrm{MeOH} + \mathrm{CO_2} \quad (\mathrm{HetNH} = \text{pyrrole}) \quad (2)$$

In a recent preliminary account, we have emphasized the potential of the reaction of pyrrole with organic carbonates for the synthesis of *N*-carbonyl compounds and reported that, in the presence of amidine (1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (**3**)) or phosphazene (*t*-butylimino-tris(dimethylamino)phosphorane (P_1-*t*-Bu) (**4**), *t*-butylimino-tris(pyrrolidino)phosphorane (BTPP) (**5**)) superbases, *N*-carbonylpyrrole derivatives can be prepared by direct reaction of pyrrole with a variety of carbonic acid diesters (dimethyl-, dibenzyl-, diphenyl carbonate, methyl phenyl carbonate, *t*-butyl phenyl carbonate) [46]. In this paper we focus on the direct reaction of pyrrole with DMC[1] in the presence of catalysts as DBU, P_1-*t*-Bu and BTPP, and fully report on the activity of the catalytic systems investigated. We show that, under the proper conditions, the reactivity of phosphazene/pyrrole/DMC system can be driven either to the selective catalytic formation of **1** or the quantitative synthesis of **2**. The nature of *N*-methylation reaction has been also explored. The fate of phosphazene catalyst has been studied and the pathway through which the catalyst deactivated under the working conditions has been rationalized.



DBU (3) P_1-t-Bu (4) BTPP (5)

2. Experimental

2.1. General

Unless otherwise stated, all reactions and manipulations were conducted under an inert gas atmosphere, by using vacuum line techniques. All solvents were dried according to literature methods [50] and stored under N_2. DMC (Fluka) was dried over 5 Å molecular sieves for 24 h, filtered, distilled, and stored under N_2. Pyrrole (Aldrich) was dried over CaH_2, filtered, distilled under vacuum over fresh CaH_2 and stored under N_2. DBU, P_1-*t*-Bu and BTPP (Fluka, Aldrich) were used as received and stored under an inert atmosphere.

GC analyses were performed with a HP 5890 Series II gas-chromatograph (capillary column: Heliflex AT-5, 30 m × 0.25 mm, 0.25 μm film thickness). GC–MS analyses were carried out with a Shimadzu GC-17A linked to a Shimadzu GC–MS QP5050 selective mass detector (capillary column: Supelco MDN-5S, 30 m × 0.25 mm, 0.25 μm film thickness). Analyses of gases were done with a Dani 8610 GC instrument equipped with a TCD 866.

IR spectra were taken on a Shimadzu FTIR Prestige 21 spectrophotometer. ^{31}P NMR spectra were run with a Bruker AM 500 spectrometer or with a Varian Inova 400 instrument. ^{31}P chemical shift are in δ (ppm) *vs* H_3PO_4 85%.

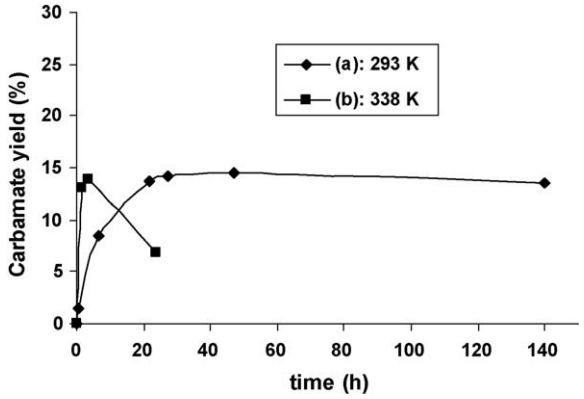


Fig. 1. Methoxycarbonylation of pyrrole with DMC in the presence of DBU (DBU/pyrrole/DMC = 1:1:3.3 mol/mol). (a) DBU: 550 μL, 3.68 mmol; pyrrole: 250 μL, 3.60 mmol; DMC: 1.0 mL, 11.88 mmol; *T*: 293 K. (b) DBU: 106 μL, 0.709 mmol; pyrrole: 49 μL, 0.706 mmol; DMC: 0.200 mL, 2.38 mmol; *T*: 338 K.

2.2. Reaction of pyrrole with DMC in the presence of DBU: general procedure

Into a Schlenk tube (20 mL), containing the solution of pyrrole in DMC, DBU and *n*-dodecane (internal standard) were added. The reaction mixture was allowed to react at the working temperature and analyzed by GC and/or GC–MS at measured intervals of time. For further details see Section 3.1 and the legend of Fig. 1.

2.3. Reaction of 1-methoxycarbonylpyrrole with methanol in the presence of DBU

Into a 10 mL tube, containing the solution of **1** (76 μL, 0.676 mmol) in anhydrous MeOH (0.200 mL, 4.9 mmol), DBU (100 μL, 0.669 mmol) and *n*-dodecane (internal standard; 20 μL, 0.088 mmol) were introduced in sequence. The solution was reacted at room temperature (293 K) and analyzed by GC and/or GC–MS at measured intervals of time. The conversion into DMC and pyrrole was as high as 97% already after 4 h and was found to be quantitative after 25 h.

2.4. Reaction of pyrrole with DMC in the presence of phosphazene bases (P_1-t-Bu or BTPP): general procedure

Into a Schlenk tube (20 mL), containing the solution of pyrrole in DMC, the used phosphazene and *n*-dodecane (internal standard) were added. The reaction mixture was allowed to react at the working temperature and monitored by GC and/or GC–MS at measured intervals of time. For further details see the legends of Figs. 2–5, 7 and 8.

[1] The reaction of pyrrole with DMC has been studied sporadically and, to date, the literature data on this process are scanty. A few early works have described the stoichiometric reaction of HetNM (HetNH = pyrrole; M = Li, Na, MgBr) salts with DMC [47] or diethyl carbonate [35,47] or *t*-butyl phenyl carbonate [48] for the synthesis of heteroaromatic carbamates HetNC(O)OR (R = Me, Et, *t*-Bu).

In a study on the utilization of DMC as methylating agent of *N*-heterocyclic compounds Thiébaud first mentioned that tetrabutylammonium chloride (8 mol%) catalyzed the reaction of pyrrole with DMC to give **2** (HetNMe) and **1** (HetNC(O)OMe) as major products [19]. By distilling MeOH as it formed, complete conversion of pyrrole was achieved after 24 h at 393 K, but the reaction was poorly selective (HetNC(O)OMe: 51%; HetNMe: 36%). At 383 K, the process exhibited higher selectivity (HetNC(O)OMe: 92%; HetNMe: 4%), but the conversion rate of pyrrole was divided by two. Afterwards, Sun has reported the synthesis of **1** from pyrrole and DMC, at 478 K, over solid bases [49]. The best results were achieved with CaO: after 3 h at 478 K, **1** was obtained in 46.7% yield, with very high selectivity (97.8%). Very recently, Gao and co-workers have briefly reported that **1** was obtained in 92% yield (after 8 h at 363 K) from pyrrole and DMC in the presence of (Bmim)OH (Bmim = 1-methyl-3-butyl imidazolium) as catalyst, without providing, unfortunately, any detail on the selectivity of the process [20].

Table 1
P_1-*t*-Bu promoted methoxycarbonylation of pyrrole with DMC in the presence of 4 Å molecular sieves, at 338 K (P_1-*t*-Bu/pyrrole/DMC = 1:1:16.8 mol/mol).

Entry	Pyrrole (mmol)	P_1-*t*-Bu (mmol)	DMC (mmol)	MS 4 Å[a] (g)	Time (h)	Yield of **1** (%)	Yield of **2** (%)	Notes
1	0.706	0.708	11.87	–	30	40	–	[b]
2	0.706	0.708	11.87	0.7705	27	64	0.5	[c]
3	0.706	0.708	11.87	1.7137	24	52	–	[d]
4	0.706	–	11.87	0.7725	17	–	–	

[a] Dried at 443 K for 3 days, before use.
[b] Under the reported reaction conditions, the decomposition of **4** was practically negligible.
[c] After 27 h under the working conditions, the GC and GC/MS analyses of the reaction mixture showed the presence of P_1-*t*-Bu and significant amounts of $OP(NMe_2)_3$.
[d] Under the working conditions, the decomposition of P_1-*t*-Bu was quantitative within 24 h.

Table 2
Decarboxylation of 1-methoxycarbonyl pyrrole (**1**) in the presence of P_1-*t*-Bu, at 393 K, in THF (1 mL).

Entry	**1** (mmol)	P_1-*t*-Bu (mol%)	Time (h)	Yield of **2** (%)
1	0.712	100	5.5	34
2	0.712	100	22.5	94
3	0.712	10	5.75	17
4	0.712	10	26	66

2.4.1. P_1-t-Bu promoted N-methoxycarbonylation of pyrrole with DMC, in the presence of 4 Å molecular sieves: general procedure

Molecular sieves 4 Å were preliminarily dried at 443 K for 3 days, cooled to ambient temperature under N_2 and handled under an inert atmosphere.

Into a Schlenk tube (20 mL), containing pretreated molecular sieves (see above), pyrrole, DMC and **4** were introduced in sequence. The reaction mixture was allowed to react at 338 K for a given time (Table 1), cooled to ambient temperature, diluted with anhydrous THF (2 mL) and filtered. After washing the molecular sieves on the filter with more THF (4 × 4 mL), the resulting solution was analyzed by GC, using *n*-dodecane (30 μL, 0.132 mmol) as internal standard.

2.5. Decarboxylation of 1-methoxycarbonyl pyrrole promoted by P_1-t-Bu

Into a Schlenk tube (20 mL), containing a THF (1 mL) solution of **1** (0.080 mL, 0.712 mmol), the phosphazene (0.180 mL, 0.708 mmol) and *n*-dodecane (internal standard; 0.050 mL, 0.22 mmol) were added. The tube was closed with a screwcap equipped with a silicon septum through which the gas phase could by sampled using an appropriate syringe. The reaction mixture was allowed to react at 393 K and, at measured times, the solution (see Table 2) and/or the gas phase were analyzed by GC. After 3 h, the amount of CO_2 present in the gas phase was equal to 0.03 mmol (4% *vs* **1**) and rised to 0.14 mmol (20% *vs* **1**) after 22.5 h.

An analogous experiment (**1**: 0.080 mL, 0.712 mmol; THF: 1 mL) was carried out using P_1-*t*-Bu in catalytic amount (0. 018 mL, 0.071 mmol, 10 mol%; see Table 2). After 26 h, the amount of CO_2 present in the gas phase was equal to 0.11 mmol (16% *vs* **1**).

3. Results and discussion

3.1. DBU promoted reaction of pyrrole with DMC

In the temperature range 293–363 K no reaction was observed between pyrrole (49 μL, 0.706 mmol) and DMC (1.0 mL, 11.88 mmol) even after long times (16 h). At 393 K, pyrrole and DMC (DMC/pyrrole: 16.8 mol/mol) reacted very slowly to give only minor amounts of **1** as the sole product (7% *vs* pyrrole, after a reaction time of 21 h).

Addition of DBU to the reacting system promoted the *N*-methoxycarbonylation process. In fact, in the presence of 1 equivalent of **3**, pyrrole and DMC (DBU/pyrrole/DMC: 1:1:3.3 mol/mol) reacted to afford **1**, even at ambient temperature (curve (a), Fig. 1). Under the above conditions, the *N*-methoxycarbonylation reaction was very selective (100%). However, the reaction proceeded slowly reaching a maximum yield of 15% after 27 h.

The process is reversible. As a matter of fact, at 293 K, in the presence of **3** (1 equivalent), **1** (76 μL, 0.676 mmol) easily reacted with an excess of MeOH (0.200 mL, 4.94 mmol), used both as reagent and solvent, to give pyrrole and DMC, quantitatively (> 99.5%, after 25 h). The amidine base, obviously, acted as a promoter also for the reverse of reaction (1), as, practically, at 293 K, in the absence of DBU, **1** did not react with methanol to give back pyrrole and DMC [46].[2]

At 338 K, the carbamation reaction (**3**/pyrrole/DMC:1:1:3.3 mol/mol) was sensibly faster than at room temperature (yield of **1**: 14% after 3.75 h; curve (b), Fig. 1). Trace amounts of **2** (<0.5%) were detected in the reaction mixture only after long reaction times (24 h). However, after the initial increase, carbamate yield decreased with time because of tendency of **1**, once formed, to react with **3** (see below). Further increase of the reaction temperature markedly lowered the selectivity of *N*-methoxycarbonylation. At 393 K, for instance, a mixture of pyrrole (49 μL, 0.708 mmol), **3** (106 μL, 0.709 mmol) and DMC (0.200 mL, 2.38 mmol; DBU/pyrrole/DMC:1:1:3.3 mol/mol) reacted to give **1** in 30% yield after 1.5 h, but the selectivity was poor because of significant formation of **2** (6% after 1.5 h). Moreover, under the latter conditions (393 K), even after a short reaction time (1.5 h), extended conversion of DBU into new species with molecular masses 166 and 224 *m/z* was observed,[3] whose formation was strongly affected by temperature, as it was less pronounced at 338 K and negligible at ambient temperature.

The ability of **1** to interact with DBU has been ascertained by reacting it with the amidine base, in the absence of solvent, under a variety of conditions (**1**/DBU = 1–10 mol/mol; 368–393 K; 1.5–24 h). In addition to the above DBU-derivatives, the GC–MS analysis of the reaction mixture showed the formation, in variable amounts depending on the used conditions, of other species such as pyrrole, **2**, DMC, 1,1′-carbonyldipyrrole. Moreover, CO_2 was found in the gas phase. Remarkably, 1-methylpyrrole always formed in minor amounts. These features suggest that DBU and **1** react in a not simple way and that, in the present case, decarboxylation of **1** to **2** is not a major reaction pathway (as a comparison, see, also, Section 3.2.1.1).

[2] An experiment analogous to that reported in the text, but carried out in the absence of DBU, showed the formation of DMC and pyrrole in trace amounts. The behaviour observed in the presence of DBU is reminiscent of that exhibited by carbamates of N-heteroaromatics different from pyrrole (indoles, imidazoles), which can be easily deprotected by methanolysis in the presence of base catalysts [51].

[3] MS (*m/z*): 166 ($M^{+\bullet}$), 151(M–CH_3), 137 (base peak), 123, 112, 97, 80, 68, 54, 42, 29. MS (*m/z*): 224 ($M^{+\bullet}$), 209, 193, 181, 165 (M–CO_2CH_3; base peak), 151, 137, 123, 112, 94, 80, 67, 54, 42, 29. As a comparison, we report also the mass spectrum of DBU (*m/z*): 152 ($M^{+\bullet}$; base peak), 137, 123, 110, 96, 82, 69, 55, 41, 29.

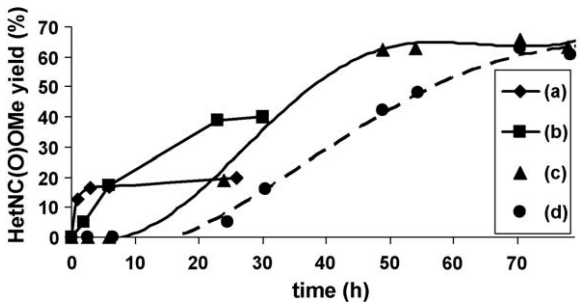


Fig. 2. Methoxycarbonylation of pyrrole (49 μL, 0.706 mmol) with DMC (residual water: 19.1 ppm, 0.0096 mol%, as determined by Karl–Fischer titration) in the presence of 1 equivalent of P_1-*t*-Bu (180 μL, 0.708 mmol), at 338 K: influence of DMC/pyrrole molar ratio. (a) DMC: 0.200 mL, 2.38 mmol; **4**/pyrrole/DMC = 1:1:3.3 mol/mol. (b) DMC: 1.0 mL, 11.88 mmol; **4**/pyrrole/DMC = 1:1:16.8 mol/mol. (c) DMC: 10 mL, 118.8 mmol; **4**/pyrrole/DMC = 1:1:168 mol/mol. (d) DMC: 10 mL, 118.8 mmol. Water (5 μL, 0.277 mmol) was added to the reaction mixture since the beginning of the run: H_2O/**4**/pyrrole/DMC = 0.39:1:1:168 mol/mol.

3.2. Reaction of pyrrole with DMC in the presence of phosphazene superbases

On the whole, the results obtained with DBU were modest mainly because of difficulty to control, under conditions (393 K) wherein we observed faster formation of **1** in higher yield (a) the selectivity of the carbamation process *vs N*-methylation; (b) the reactivity of DBU with **1**. Nevertheless, the above results indicate that, in principle, superbase organo-catalysts may be active in promoting reactions (1) and (2). We considered, therefore, superbases different from DBU, such as the sterically hindered phosphazenes P_1-*t*-Bu and BTPP [52–55].

3.2.1. Catalytic activity of P_1-t-Bu

The activity of P_1-*t*-Bu has been investigated in the range 293–423 K under various conditions. At ambient temperature (293 K), likewise DBU, also P_1-*t*-Bu (0.180 mL, 0.708 mmol) promoted selectively (100%) the carbamation of pyrrole (49 μL, 0.708 mmol) with DMC (0.200 mL, 2.38 mmol; **4**/pyrrole/DMC = 1:1:3.3 mol/mol), but in low yield (12%, after 24 h).

At 338 K, keeping constant the molar ratio **4**/pyrrole/DMC (1:1:3.3 mol/mol), carbamate yield increased to 17% within 6 h (Fig. 2(a)) and, differently from the corresponding reaction with DBU (for a comparison, see also Fig. 1(b)), did not decrease upon prolonging the reaction time. The methoxycarbonylation reaction was very selective (100%), as no formation of either **2** or any other methyl or carbonylpyrrole derivative was observed even after prolonged heating (26 h) at the working temperature (338 K).

Fig. 2 summarizes the behaviour of the reacting system at 338 K, when, using 1 equivalent of **4** (*vs* pyrrole), the DMC/pyrrole molar ratio was varied. Using a **4**/pyrrole/DMC molar ratio of 1:1:16.8 mol/mol (Fig. 2(b)) slowed down the carbamation process because of the lower concentration of P_1-*t*-Bu and pyrrole, but increased the carbamate yield which was as high as 40% after 30 h. No formation of HetNMe was observed under these conditions. An even higher yield (63%) was achieved using a larger excess of DMC (**4**/pyrrole/DMC = 1:1:168 mol/mol), but after longer reaction times (54 h; Fig. 2(c)). The incidence of *N*-methylation process was negligible (traces) even after very long times. Under the latter conditions, involving a greater dilution of reactants (pyrrole, **4**), the methoxycarbonylation reaction showed an induction period, which may be due to residual water present in DMC (used, in the latter case, in larger excess (10 mL) with respect to the other reactants). Accordingly, the induction time increased when, under otherwise identical reaction conditions, water was deliberately added to the reacting system since the beginning of the run (Fig. 2(d)).

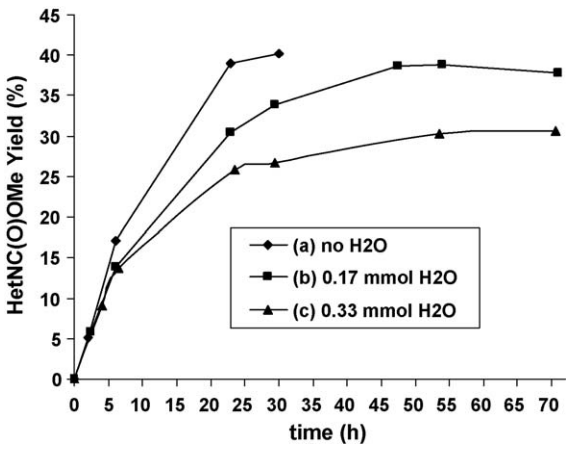


Fig. 3. Methoxycarbonylation of pyrrole (49 μL, 0.706 mmol) with DMC (1.0 mL, 11.88 mmol; residual water: 19.1 ppm, 0.0096 mol%, as determined by Karl–Fischer titration) in the presence of 1 equivalent of P_1-*t*-Bu (180 μL, 0.708 mmol), at 338 K (**4**/pyrrole/DMC = 1:1:16.8 mol/mol). Influence of added water. (a) No H_2O was added. (b) H_2O (3 μL, 0.167 mmol) was added; H_2O/**4**/pyrrole/DMC = 0.24:1:1:16.8 mol/mol. (c) H_2O (6 μL, 0.333 mmol) was added; H_2O/**4**/pyrrole/DMC = 0.48:1:1:16.8 mol/mol.

However, no detectable induction period was observed at more elevated concentrations of reactants (Fig. 2(a) and (b) or Fig. 3(a)), even in the presence of added H_2O (Fig. 3(b) and (c)). In the latter cases, addition of water slowed down the conversion rate and lowered the yield of carbamate product (Fig. 3(b) and (c)), showing, thus, that the *N*-methoxycarbonylation reaction is a water-sensitive process.

The carbamation process was investigated in the presence of 4 Å molecular sieves, used in this context mainly for their ability to act as MeOH sequestering agents [56]. Table 1 summarizes the results obtained when the system **4**/pyrrole/DMC (1:1:16.8 mol/mol) was reacted at 338 K in the presence of 4 Å MS. As expected, the addition of the molecular sieves improved the yield of **1** (compare, for instance, entry 2 and entry 1, in Table 1). We can exclude that, under the working conditions, molecular sieves can play any catalytic role. In fact, no reaction was observed when pyrrole and DMC were reacted at 338 K in the presence of 4 Å MS, but in the absence of **4** (entry 4, Table 1).

Both yield and selectivity observed in the presence of MS were remarkable also in virtue of the fact that they were achieved under very mild conditions (338 K), within reasonable reaction times (∼1 day). However, a major drawback relevant to the use of molecular sieves was the extended decomposition of **4** to $OP(NMe_2)_3$ and other unidentified P-species, which, conversely, was much lesser or negligible when molecular sieves were not used (entry 1, Table 1). This different behaviour may be related mainly with the tendency of DMC to decompose with generation of CO_2 when heated over MS, as we have ascertained separately,[4] and to the reactivity exhibited by phosphazenes in the presence of CO_2 (see Section 3.2.1.2). The higher the 4 Å MS/DMC weight ratio, the more pronounced the generation of CO_2 and the faster the decomposition of a given amount of **4** (0.706 mmol, Table 1): this may explain why in entry 3 of Table 1 (MS/DMC/**4** = 1.60:1:0.16 wt/wt) carbamate yield was lower than in entry 2 (MS/DMC/**4** = 0.72:1:0.16 wt/wt), despite the higher amount (more than twice) of molecular sieves employed.

[4] A suspension of 4A MS (0.6168 g; dried at 443 K for 3 days, before use) in DMC (2 mL) was stirred at 338 K for 22 h in a closed vessel, under a dinitrogen atmosphere. The GC and GC–MS analysis of the gas phase showed the presence of CO_2, which was detected also in solution by means of FTIR spectroscopy (2340 cm^{-1}). No evidence of CO_2, either in gas phase or in solution, was found, when, as a blank, THF, instead of DMC, was used as the solvent.

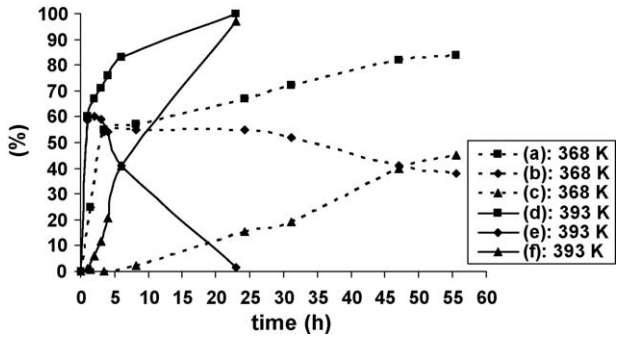


Fig. 4. Methoxycarbonylation of pyrrole (49 μL, 0.706 mmol) with DMC (1.0 mL, 11.88 mmol) in the presence of P_1-*t*-Bu (180 μL, 0.708 mmol), at 368 K ((a)–(c)) and 393 K ((d)–(f)) (**4**/pyrrole/DMC = 1:1:16.8 mol/mol). (a) and (d): pyrrole conversion. (b) and (e): carbamate yield. (c) and (f): 1-methylpyrrole yield.

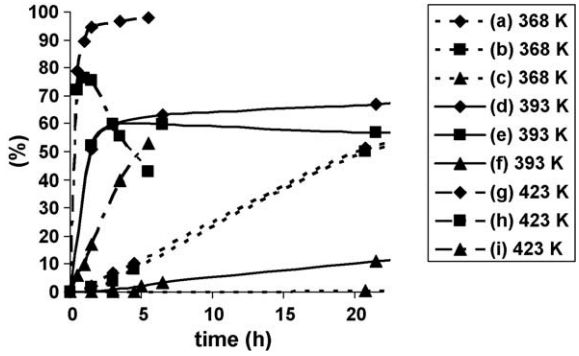


Fig. 5. Methoxycarbonylation of pyrrole (49 μL, 0.706 mmol) with DMC (1.0 mL, 11.88 mmol) in the presence of P_1-*t*-Bu (18 μL, 0.0708 mmol) (**4**/pyrrole/DMC = 0.1:1:16.8 mol/mol), at 368 K (a)–(c), 393 K (d)–(f) and 423 K (g)–(i). (a), (d) and (g): pyrrole conversion; (b), (e) and (h): carbamate yield; (c), (f) and (i): 1-methylpyrrole yield.

The reactivity of system P_1-*t*-Bu/pyrrole/DMC has been investigated also at temperatures higher than 338 K. Fig. 4 summarizes the results obtained at the temperatures of 368 and 393 K, using a P_1-*t*-Bu/pyrrole/DMC molar ratio equal to 1:1:16.8 mol/mol. At both temperatures the conversion into **1** reached a maximum value around 60% within relatively short times and, then, decreased with time. The diminution of the carbamate yield was accompanied by progressive increase of formation of 1-methylpyrrole with consequent lowering of selectivity with time.

Remarkably, after 23 h at 393 K, conversion of pyrrole into 1-methylpyrrole was practically quantitative (97%). The above result deserves attention as it demonstrates that, in the presence of phosphazenes, DMC can be used in the *direct* reaction with pyrrole not only as a suitable *carbonylating agent* succedaneous for phosgene, but also as safe innocuous and selective *N-methylating agent* in place of CH_3X and $(MeO)_2SO_2$ (see also Section 3.2.2).

The behaviour of reacting system was studied also in the presence of sub-stoichiometric amounts of the phosphazene. Fig. 5 illustrates the results obtained at 368, 393 and 423 K, when a lower catalyst loading (10 mol% *vs* pyrrole) was used, without varying the pyrrole/DMC molar ratio (1:16.8 mol/mol). At 368 K the *N*-methoxycarbonylation process is very selective (>99%) but quite slow, whereas, at 423 K, albeit much faster and effective, is not enough selective (92%) even after very short reaction times (0.5 h). Remarkably, at 393 K, highly selective (99%) conversion of pyrrole into carbamate **1** (60% yield) was achieved within only 3 h.

3.2.1.1. N-methoxycarbonylation vs N-methylation: factors affecting carbamate selectivity. Under the conditions employed in the present study, we have never observed the formation of by-products involving the functionalisation of the carbon atoms of pyrrole ring. Such species may form in variable amounts, depending on the conditions employed, when HetNM salts (M = Li, Na, K, MgX) have been reacted stoichiometrically with organic carbonates [35,47] or chloroformates [35]. The selectivity of the carbamation process (Eq. (1)) was, therefore, closely related with the incidence of *N*-methylation reaction (Eq. (2)).

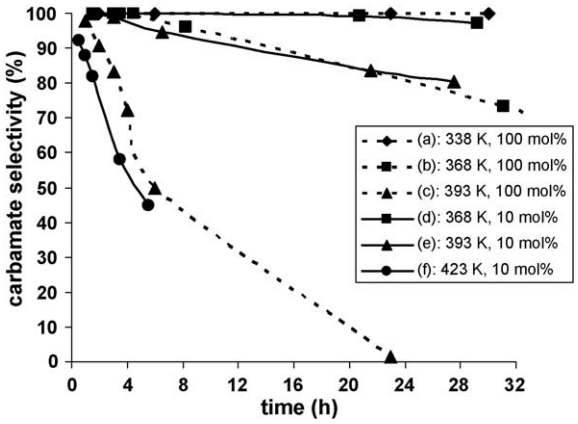


Fig. 6. Methoxycarbonylation of pyrrole (49 μL, 0.706 mmol) with DMC (1.0 mL, 11.88 mmol) in the presence of P_1-*t*-Bu: influence of reaction time, temperature and catalyst loading on carbamate selectivity. (a)–(c) P_1-*t*-Bu: 180 μL, 0.708 mmol; **4**/pyrrole/DMC = 1:1:16.8 mol/mol. (d)–(f) P_1-*t*-Bu: 18 μL, 0.071 mmol; **4**/pyrrole/DMC = 0.1:1:16.8 mol/mol.

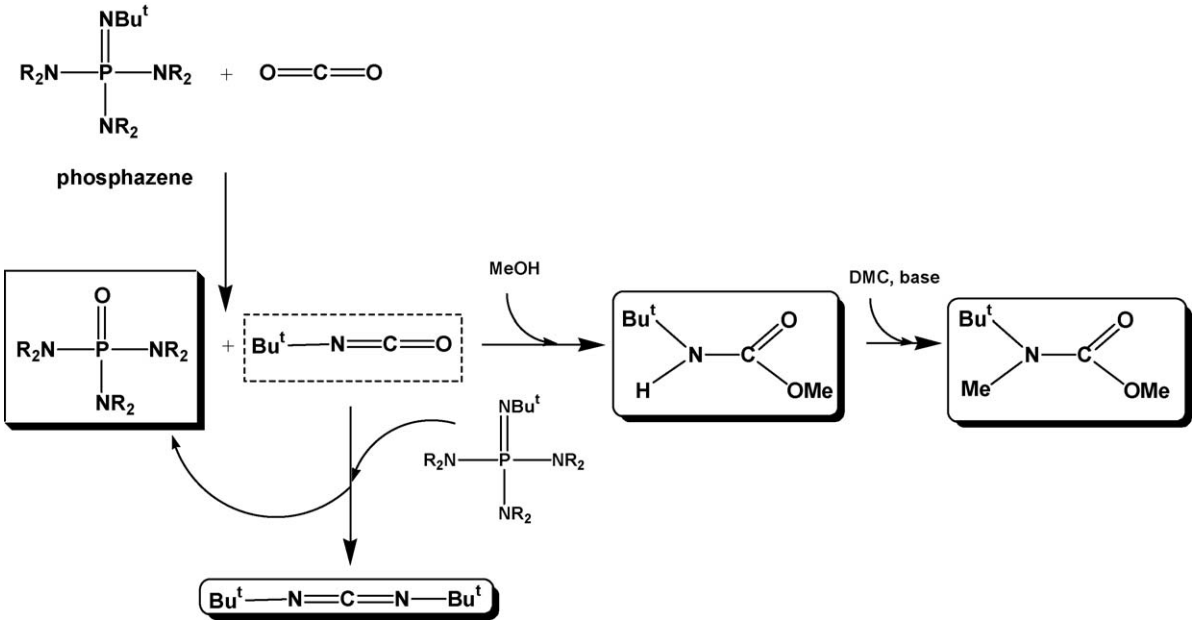
While methoxycarbonylation is a reversible process (see Section 3.1), the methylation reaction takes place irreversibly [11,15]. *Per sè*, these different features of the two processes may provide a first simple rationale to the fact that carbamate selectivity, in general, decreases with reaction time (Fig. 6).

The decrease of selectivity with time is strongly affected by reaction temperature. For instance, in the presence of 1 equivalent of **4** (Fig. 6(a)–(c)), the diminution of selectivity was relatively steep at 393 K, more gradual at 368 K, null at 338 K. On this basis, it can be inferred that *N*-methylation of pyrrole with DMC requires a higher energy input than *N*-methoxycarbonylation and is more efficiently promoted at relatively more elevated temperatures.

Fig. 6 also shows that, at a given temperature, the diminution of selectivity with time also depends on the amount of catalyst used. The higher the catalyst load, the faster the decrease of selectivity with time (in Fig. 6, compare (b) and (c) with (d) and (e), respectively). It is, therefore, possible that also the *N*-methylation rate depends on the catalyst concentration and, not only *N*-methoxycarbonylation, but also *N*-methylation is promoted by the phosphazene catalyst.

The nature of *N*-methylation reaction has been examined more closely. The experimental data show that *N*-methoxycarbonylation is a faster process than *N*-methylation. In those cases where **2** forms in significant yield (Figs. 4 and 5(d)–(f), (g)–(i)), the comparative analysis of the curves of formation of **1** and **2** clearly indicates that **1** tends initially to accumulate in the reaction mixture until a maximum yield is reached, but, afterwards, diminishes progressively with time. The disappearance of **1** is accompanied by the formation of **2**, which, accordingly, shows a variable induction period, depending on the working conditions (temperature, catalyst loading). These facts suggest that **1** may be a stable intermediate in the formation of **2** and **2** may form from **1** through a decarboxylation reaction (Eq. (3)), which, as noted above, may be promoted by the phosphazene catalyst.

$$\mathrm{HetNC(O)OMe} \rightarrow \mathrm{HetNMe} + \mathrm{CO_2} \qquad (3)$$



Scheme 1.

Both these issues have been elucidated by *ad hoc* studies. Carbamate **1** (0.050 mL, 0.445 mmol), when heated at 393 K for 6 h in DMC (1 mL, 11.88 mmol), did not convert into **2**. This result ruled out that **2** may form by simple thermal decarboxylation of **1**. However, when **1** (0.081 mL, 0.712 mmol) was heated in THF (1 mL) at 393 K, in the presence of P_1-*t*-Bu, **2** formed in yields significant also from a synthetic point of view (Table 2). According to reaction (3), in these experiments CO_2 was also generated and has been detected by means of GC analysis of the gas phase (see also Section 2.5).

Table 2 shows that in the presence of an equimolar amount of **4** (entries 1 and 2), the decarboxylation of **1** was practically quantitative within 24 h and faster than with a phosphazene load of 10 mol% *vs* pyrrole (Table 2, entries 3 and 4). In the latter case, the conversion of **1** into **2** was not only slower but also not complete (66%) after 26 h, as a consequence of the fact that, after this time, under the working conditions (**4**: 10 mol%; 393 K), deactivation of the phosphazene base (upon reaction with CO_2; see also Section 3.2.1.2) was practically quantitative. Accordingly, protracting heating longer at the working temperature (393 K) did not cause any further significant increase of the conversion of **1** into **2**. The HetNMe yield (66%) observed in the latter experiment, albeit less attractive from a synthetic standpoint, is very informative as demonstrates clearly that the decarboxylation reaction is not a stoichiometric process with respect to **4**, but proceeds catalytically.

As a whole, the above data allow to conclude that (a) in the presence of phosphazene, the decarboxylation of 1-methoxycarbonyl pyrrole is a major reaction pathway to the formation of 1-methylpyrrole differently from what observed with DBU, and (b) also this process can be catalytically promoted by the phosphazene catalyst.

3.2.1.2. Deactivation of phosphazene. The stability of the phosphazene catalyst, under the employed conditions, depends, critically, on the working temperature, which, therefore, controls, significantly, not only yields and selectivities, but also the deactivation of catalyst. The higher the temperature, the lower the carbamate selectivity and, for a given reaction time, the more extended the deactivation of the phosphazene catalyst. At ambient temperature, for instance, no evidences of P_1-*t*-Bu decomposition were observed by GC or GC–MS, even after long reaction times. At 393 K (Figs. 4(d)–(f)) and 5(d)–(f)), the decomposition of **4** was evident, but of modest importance, since the first 2–3 h, and became larger and larger with time. After about 24 h at 393 K, the decomposition of **4** was practically complete (Fig. 5(d)–(f)) or, anyhow, in a very advanced stage (Fig. 4(d)–(f)). The GC–MS analysis of the reaction mixtures showed the major formation of $OP(NMe_2)_3$, which did not exhibit any catalytic activity,[5] and other species, such as, for instance (*t*-Bu)NHC(O)OMe, (*t*-Bu)N(Me)C(O)OMe, and (*t*-Bu)NCN(*t*-Bu).[6]

The generation of CO_2 by decarboxylation of **1** may open a way to the deactivation of the phosphazene into $OP(NMe_2)_3$ and lead, through the intermediacy of co-produced (*t*-Bu)NCO, to the formation of the other observed products (Scheme 1).[7]

The ability of phosphazenes, such as **4** or **5**, to convert into $O=P(NR_2)_3$ (R = Me, C_4H_8) and (*t*-Bu)NCO by reaction with CO_2 has been ascertained in *ad hoc* experiments. For instance, upon saturating a THF-d_8 solution of **4** with carbon dioxide, at ambient temperature (293 K), the ^{31}P NMR(162 MHz) resonance of **4**, at 1.77 ppm, disappeared and was replaced by a new signal at 24.48 ppm due to $OP(NMe_2)_3$, whose formation was further confirmed also by GC–MS analysis of the reaction solution. Analogously, at ambient temperature (293 K), in anhydrous THF (2.5 mL), BTPP (0.072 mL, 0.24 mmol) easily reacted with an excess of CO_2 (1 atm) to give $OP(NC_4H_8)_3$ (confirmed by GC–MS) and (*t*-Bu)NCO. The presence of (*t*-Bu)NCO was easily demonstrated by IR analysis of the reaction mixture, whose spectrum showed a very strong absorption at 2257 cm^{-1}, which was diagnostic of the NCO group of the organic isocyanate [57].

The formation of the isocyanate (*t*-Bu)NCO may easily account for the generation of the other observed products (Scheme 1). The formation of carbodiimides by aza-Wittig reaction of isocyanates with iminophosphoranes is a process well documented in the

[5] In a few dedicated experiments we have verified that, at 393 K, $OP(NMe_2)_3$ did not promote either reactions (1) and (2) or reaction (3).

[6] MS (*m*/*z*) of (*t*-Bu)NHC(O)OMe: 131 ($M^{+\bullet}$), 116 (M–CH_3, base peak), 100, 73, 72, 57, 41. MS (*m*/*z*) of (*t*-Bu)MeNC(O)OMe: 145 ($M^{+\bullet}$), 130 (M–CH_3), 114 (M–OMe), 86 (M – CO_2Me), 73 (base peak), 57, 56, 41. MS (*m*/*z*) of (*t*-Bu)NCN(*t*-Bu): 154 ($M^{+\bullet}$), 139 (M–CH_3), 97 (M–*t*-Bu), 83 (M– *t*-BuN), 57 (base peak), 41.

[7] In both the experiments described in Table 2 (see also Sections 2.5 and 3.2.1.1) we have observed also the formation of significant amounts of both $OP(NMe_2)_3$ and (*t*-Bu)NCN(*t*-Bu).

literature [58]. Moreover, the reaction of (*t*-Bu)NCO with MeOH co-produced in the catalytic process (Eq. (1), R = Me) may easily explain the formation (*t*-Bu)NHC(O)OMe [59], which, by reaction with DMC in the presence of base, can afford (*t*-Bu)N(Me)C(O)OMe [11].

3.2.2. Catalytic activity of BTPP

The catalytic behaviour of P_1-*t*-Bu ($^{MeCN}pK_a$ = 26.88) has been compared with that of BTPP ($^{MeCN}pK_a$ = 28.35), which is not only a stronger base than **4**, but also a more powerful nucleophile [54,55].

BTPP (**5**) proved to be a more active catalyst than P_1-*t*-Bu (**4**), in accordance with its higher basicity and nucleophilicity. Fig. 7 allows to compare the catalytic activity of **5** and **4** at 393 K, when they were used in equimolar amount *vs* pyrrole, under otherwise analogous conditions (phosphazene/pyrrole/DMC = 1:1:16.8 mol/mol). BTPP promoted the conversion of pyrrole into **1** and **2** more effectively than P_1-*t*-Bu.

In the presence of **5**, the conversion of pyrrole into the ultimate product, 1-methylpyrrole, was practically quantitative within 6 h. Fig. 8 shows the results obtained with BTPP at 393 and 423 K, using 10 mol% of catalyst (*vs* pyrrole) and a 1:16.8 pyrrole/DMC molar ratio.

At the highest temperature (423 K), a very high conversion (87%) of pyrrole was already achieved in a short time (0.5 h), but with poor carbamate selectivity (87%) because of side-formation of **2**. Prolonging heating at the working temperature, **2** was obtained in quantitative yield from pyrrole and DMC in only 3 h. This result is worth noting, as, to date, literature does not provide better examples of catalytic *N*-methylation of pyrrole with DMC, characterized by a so high yield and selectivity (≈100%).

At 393 K (Fig. 8), the *N*-methoxycarbonylation proceeded more selectively than at 423 K. Remarkably, after 3 h, **1** formed with excellent selectivity (98%), in yield (66%) higher than that achieved with **4** (60%) under identical conditions (*3.2.1*). A slightly higher yield (68%) was achieved after 6.5 h, but selectivity was less satisfactory (95%). Curves (c) and (d) in Fig. 9 show that, under the working conditions (393 K; 10 mol% catalyst; catalyst/pyrrole/DMC = 0.1:1:16.8 mol/mol), **5** and **4** exhibit a very similar carbamate selectivity. However, at higher temperature (Fig. 9(e)–(f): 423 K; 10 mol% catalyst; catalyst/pyrrole/DMC = 0.1:1:16.8 mol/mol) or with a more elevated catalyst loading (Fig. 9(a)–(b): 393 K; 100 mol% catalyst; catalyst/pyrrole/DMC = 1:1:16.8 mol/mol) the carbamate selectivity decreases with time faster for **5** than for **4**. This feature may find a rationale in the higher activity (both methoxycarbonylating and methylating) of **5** with respect to **4**.

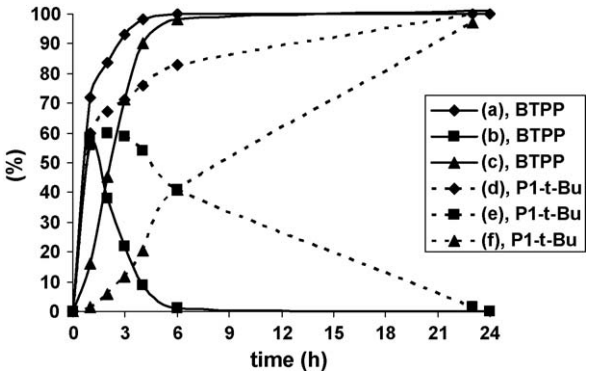


Fig. 7. Methoxycarbonylation of pyrrole (49 μL, 0.706 mmol) with DMC (1.0 mL, 11.88 mmol) in the presence of BTPP (215 μL, 0.703 mmol; (a)–(c)) or P_1-*t*-Bu (180 μL, 0.708 mmol; (d)–(f)), at 393 K (phosphazene/pyrrole/DMC = 1:1:16.8 mol/mol). (a) and (d): pyrrole conversion; (b) and (e): carbamate yield; (c) and (f): 1-methylpyrrole yield.

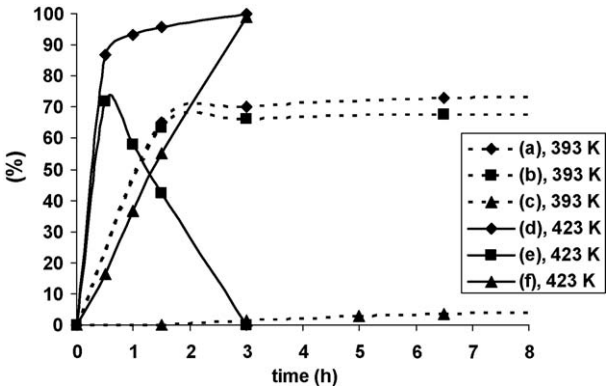


Fig. 8. Methoxycarbonylation of pyrrole (49 μL, 0.706 mmol) with DMC (1.0 mL, 11.88 mmol) in the presence of BTPP (22 μL, 0.072 mmol) (**5**/pyrrole/DMC = 0.1:1:16.8 mol/mol), at 393 K, (a)–(c), and at 423 K, (d)–(f). (a) and (d): pyrrole conversion; (b) and (e): carbamate yield; (c) and (f): 1-methylpyrrole yield.

As for the catalyst stability (see also Section 3.2.1.2), **5** exhibited a behaviour close to that shown by **4**. At 393 K, for instance, deactivation of **5** into $OP(NC_4H_8)_3$ was still modest within 1.5–3 h, wherein the best carbamate yields with the highest selectivities were observed. In principle, after this time the active catalyst can be recovered to be reused. The recovery of the active catalyst in quantitative yield was particularly straightforward in the case of BTPP because of its low volatility and was easily achieved by distilling under vacuum the reaction mixture at ambient temperature. The distillate, collected into a trap dipped in a liquid nitrogen bath, contained the reaction products (**1**, MeOH), unreacted pyrrole and the excess of DMC as main components, but not BTPP, as ascertained by GC. BTPP, together with formed $OP(NC_4H_8)_3$, was the major component of the poorly volatile distillation residue.

3.2.3. Role of phosphazene catalyst

In principle, two different roles can be envisaged for the phosphazene catalyst.

Phosphazene may act as a base and activate the *N*-heteroaromatic substrate HetNH by converting it into pyrryl anion, a stronger nucleophile than pyrrole (Scheme 2). A base catalysis has been proposed by Sun and co-workers for the *N*-methoxycarbonylation of pyrrole over solid base (CaO) catalysts [49].

However, phosphazene may also act as a nucleophile rather than as a base and activate the organic carbonate through the intermediate formation of a carbamate substituted phosphonium salt (**A**), which may convert, through an acid–base reaction with free pyrrole, into the ion pair (**B**), a potential precursor of both **1** and **2** (Scheme 3). Nucleophilic activation of DMC and other carbonic acid diesters $(RO)_2CO$ [14,17,60–64] by formation of (**A**)-

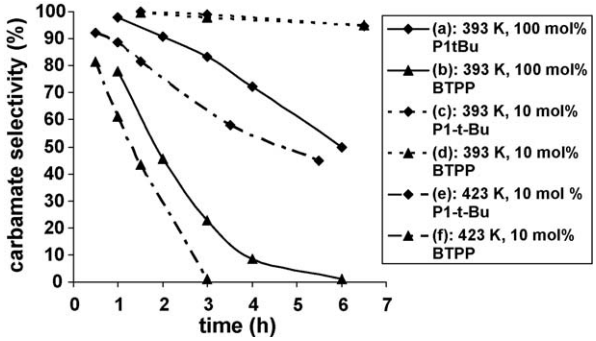
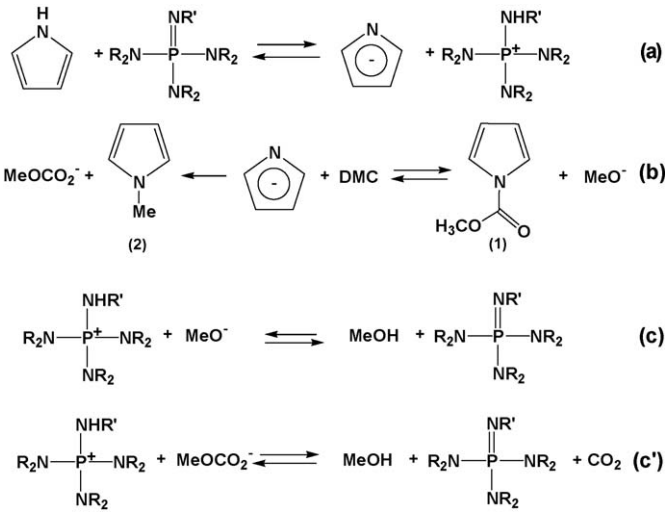


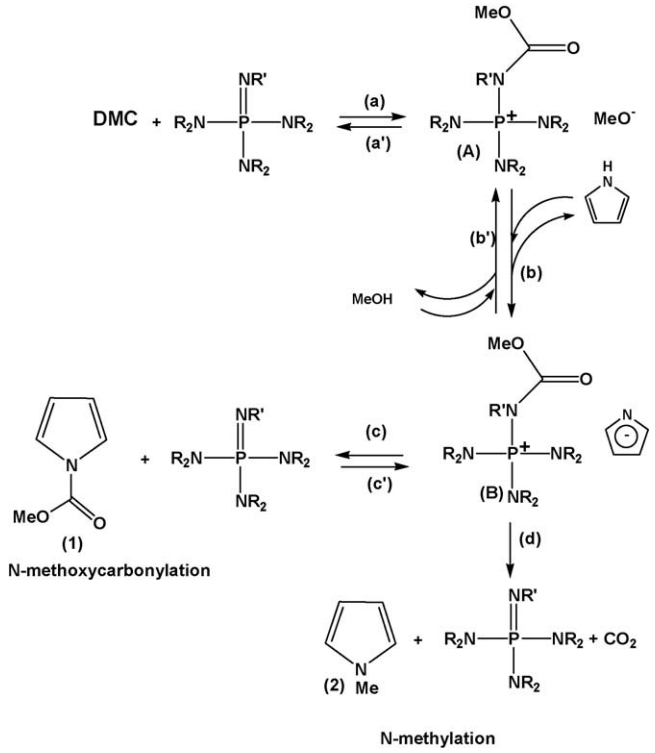
Fig. 9. Methoxycarbonylation of pyrrole (49 μL, 0.706 mmol) with DMC (1.0 mL, 11.88 mmol) in the presence of P_1-*t*-Bu (a), (c) and (e) or BTPP (b), (d) and (f). Carbamate selectivity *vs* time.



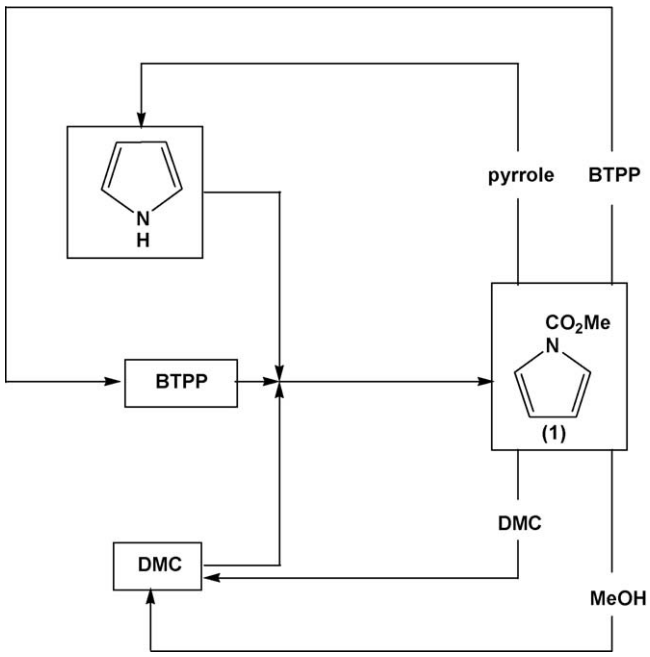
Scheme 2. Base catalysis.

like [Nu-C(O)OR]$^{n+}$ species (n = 1, Nu (nucleophile) = DABCO [17], DBU [14,64], TBD (1,5,7-triazabicyclo[4.4.0]dec-ene) immobilized on mesoporous MCM-41 silica [61]; n = 0, Nu = $X_2PO_2^-$ (X = Ph, PhO, BuO) [60,62,63]), even at temperature as low as 363–368 K [14,17,64], is well documented in the literature. The catalyst may activate nucleophilically also the primary product **1** to give back (**B**) (Scheme 3, step (c′)). This is fully consistent with the reversible nature of the *N*-methoxycarbonylation process and provides an easy rationale for the fact that **2** can form by the irreversible decarboxylation of **1** in the presence of phosphazene (Scheme 3, steps (c′) and (d)).

Both mechanistic pathways (Schemes 2 and 3) are at present under investigation.



Scheme 3. Nucleophilic catalysis.



Scheme 4.

4. Conclusions

P_1-*t*-Bu and BTPP phosphazenes have been investigated as catalysts for direct reaction of pyrrole with DMC. This work shows that the system phosphazene/pyrrole/DMC exhibits high synthetic versatility, as, depending on the reaction conditions, it is a useful flexible tool, not only for the direct and selective phosgene-free synthesis of **1**, but also for the straightforward and selective *N*-methylation of the heteroaromatic ring through a safer way which avoids the use of harmful methylating agents such as methyl halides and $(MeO)_2SO_2$. BTPP showed a higher catalytic activity than P_1-*t*-Bu in accordance with the higher basicity and stronger nucleophilicity. The other superbase investigated, DBU, is not as effective as **4** or **5**.

The factors allowing to drive the reactivity of phosphazene/pyrrole/DMC system to the selective formation of either **1** or **2** have been characterized.

Selective *N*-methoxycarbonylation of pyrrole to **1** is favoured by relatively low temperatures (293–393 K), shorter reaction times, relatively lower catalyst loadings. Accordingly, after 3 h at 393 K, in the presence of catalytic amounts of **4** or **5** (10 mol%), **1** can be obtained directly from pyrrole and DMC (1:16.8 mol/mol) with very high selectivity (≥98%), never documented so far, and yields (60–66%) satisfactory from the synthetic point of view. After short times (≈3 h) at 393 K, deactivation of catalyst is still moderate as to make meaningful the catalyst recovery, which can be very easily accomplished in the case of BTPP. In principle, also unreacted pyrrole and the organic carbonate can be recovered and recycled, as well as co-produced MeOH which is a starting material for the synthesis of DMC [2,3] (Scheme 4). These features make the process attractive from the environmental sustainability point of view.

Higher reaction temperatures (393–423 K), longer reaction times, higher phosphazene loadings favour *N*-methylation of pyrrole with respect to *N*-methoxycarbonylation. We have ascertained that a major reaction pathway to the formation of **2** involves the decarboxylation of the primary product **1**. Under conditions particularly favourable for *N*-methylation (high temperature and/or high catalyst loading), also the nature of

phosphazene catalyst can play an important role (Fig. 9(a), (b) and (e), (f)): in fact, the more active the phosphazene catalyst, the more effective the *N*-methylation process. Accordingly, at 423 K, in the presence of 10 mol% of BTPP, pyrrole can be quantitatively methylated to 1-methylpyrrole within 3 h. This finding does not find a better precedent in the literature, and provides the first example of selective and quantitative conversion of pyrrole to **2** by catalytic *N*-methylation of the heteroaromatic ring with dimethyl carbonate.

Acknowledgements

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